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(54) Title: MICROCAPSULES BY COACERVATION CONTAINING A PHARMACEUTICAL INCORPORATED IN THE
COATING POLYMER

(57) Abstract: Microcapsules containing an active ingredient, constituted by a core coated with a polymer membrane, characterized
in that the active ingredient is incorporated in the polymer-coating layer, and in that said layer is applied using microencapsulation
techniques (coacervation by means of phase separation). The microcapsules; thus produced have excellent properties of taste mask-
ing and prolonged release of the active ingredients.

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**MICROCAPSULES BY COACERVATION CONTAINING A PHARMACEUTICAL
INCORPORATED IN THE COATING POLYMER****Field of the Invention**

The present invention relates to the field of microcapsules.

5 Prior art

The coating of inert cores with active ingredients is a well known method in the pharmaceutical field and it is generally carried out using coating pans or fluid beds. The coating may be applied through a powder layering process or a solution layering process. In both techniques the application of the active principle
10 to the surface of inert beads is carried out by means of a binder.

This type of formulation in microcapsules is generally used in order to increase the exposure of the active principle to the aqueous medium and thus to increase the bioavailability of poorly soluble drugs.

Also known is the art is the possibility to modulate the release of this type of
15 formulations by covering the layer of active principle with a further film (US 6,077,533) containing a polymer that controls release, masks the unpleasant taste or, yet again, isolates the active ingredient from direct exposure to light or air.

Furthermore, in US 4,261,971 it is disclosed a gastro-resistant formulation obtained by coating the surface of a core of inert material by a solution layering
20 process, wherein a solution comprising an active principle and a gastro-resistant polymer is sprayed on the inert cores in a fluid bed apparatus.

A well known technique used for the preparation of microcapsules is the coating of crystals or granules containing active substances by coacervation by phase separation in order to provide them with taste masking or modified release
25 properties (U.S. Pat. No. 4,411,933; U.S. Pat. No. 3,860,733). This process may take place both in an aqueous environment and in an organic solvent. In the first case, the polymer is separated from the solution by modifying its solubility either by means of variations in the pH and/or temperature or by adding phase-separation inducing agents to the solutions; in the second case separation of the
30 polymer is obtained by a variation in solubility caused by variation in the temperature of the solution in which the polymer is dissolved.

The above described powder layering processes performed by applying the active ingredient with fluid bed apparatus or coating pans are time consuming and are relatively costly multi-step processes. Often the therapeutic dose of the pharmaceutical is very small, for example from 1 to 10 mg: the production of granules or pellets with a small active ingredient content could create problems of content uniformity. Moreover, loading the active ingredient on cores by powder layering, in the case of low dosage substances, requires the formulation of mixtures of powders with extremely low active ingredient concentrations to guarantee homogeneous distribution on the substrate; this requires the use of large volumes of diluents and very long coating times, which is reflected in high process costs. If on the other hand microcapsules containing only the active ingredient were to be produced problems of dosage would still be created due to the need for a high level of dilution of the microcapsules in the final pharmaceutical form.

Therefore, new procedures with improved efficiency are still required to deposit pharmaceutical particles on cores, in particular a procedure with high repeatability and low industrial cost that guarantees uniform deposition of pharmaceutical particles on the surfaces of cores, even when working with very small doses of pharmaceutical.

Summary of the invention

It has now surprisingly been found that, using the technique of microencapsulation by coacervation by means of phase separation, it is possible to produce microcapsules with a core consisting for example of a granule, a non-pareil, a pellet of excipient, usually of inert material, which is coated with a polymeric membrane wherein the active ingredient is dispersed in the form of solid particles.

The microcapsules thus produced may advantageously carry the active substances in taste-masking and/or modified release formulations.

The procedure to obtain the aforesaid microcapsules consists essentially in producing a homogeneous solution of the coating polymer in a suitable solvent in which the cores to be coated, the particles of active ingredient and, optionally,

membrane additives are dispersed in suspension. Per se known methods are then used to cause insolubilisation of the polymer, which gels (coacervates) around the cores to form the microcapsules. For example, phase separation may be performed through variation in temperature or in pH or by adding phase-
5 separation inducing substances that cause insolubilisation of the polymer. Finally, the microcapsules obtained are subjected to hardening, if required, and recovered.

The fact that the solution subjected to coacervation not only contains the customary membrane agents, but also the pharmaceutical particles which,
10 following coacervation, are incorporated into the coating layer of the cores, is characteristic of the present invention.

The solvent utilised in the coacervation procedure is chosen so as to dissolve the coating polymer but not the active ingredient(s), the membrane additive(s) and the inert cores.

15 In the case of coating polymers insoluble in water, the coacervation solvent is an organic solvent, such as cyclohexane, or a mixture of organic solvents; in the case of coating polymers soluble in aqueous medium, the coacervation solvent is preferably water with the addition of buffer salts if required.

Among the additives that may be used in an organic solvent environment we may
20 cite lactose, mannitol or water-soluble polymers such as polyvinylpyrrolidone and its derivatives or cellulose derivatives such as HPMC, MC, HPC. Other additives to use in an organic environment that may be included in the membrane together with the active ingredient may be fast swelling ones such as sodium carboxymethylamide (Explotab), croscarmellose (AcDiSol), Crospovidone,
25 pregelatinized starch (Starch 1500). Also included in the membrane may be pH modifiers (organic acids, bases, salts, buffer systems) with the aim of facilitating complete dissolution and diffusion of the active ingredient.

Among the excipients that can be used in an aqueous solvent environment we can cite calcium and magnesium salts such as dibasic calcium phosphate,
30 calcium sulphate, barium sulphate, calcium carbonate, magnesium carbonate and silicates.

Phase separation is performed with per se known means, for example through variation in temperature or in pH, or by adding phase-separation inducing substances that cause insolubilization of the polymer. The microcapsules obtained are then subjected to hardening, if required, and finally recovered.

5 **Description of the figures**

Figure 1 shows a microscope image of a microcapsule obtained in accordance with Example 3 of the present invention.

Figure 2 shows a microscope image of a microcapsule obtained in accordance with Example 11 of the present invention.

- 10 Figure 3 shows a microscope image of a microcapsule obtained in accordance with Example 8 of the present invention.

Detailed description of the invention

- The present invention relates to a method of preparing microcapsules containing at least one active ingredient comprising the application of a polymeric membrane containing at least one active ingredient and, optionally, at least one membrane additive to a core having dimensions ranging from 50 to 1200 μm wherein said application is carried out by the process of coacervation by means of phase separation.
- 15

- The microcapsules obtained with the process of the invention are characterised by the dispersion of the active ingredient(s) and, if required, membrane additive(s) in the polymeric membrane in the form of solid particles.
- 20

- Microencapsulation by phase separation is a per se known procedure. The present invention is characterised by the fact that the coacervation solution contains, in addition to the customary membrane agents, also active ingredient particles, suspended therein, which, following coacervation, are incorporated in the coating membrane of the cores.
- 25

More specifically, the procedure according to the invention comprises the following steps:

- (a) forming a solution of the coating polymer in an aqueous or in organic solvent;
- 30 (b) suspending the cores, the particles of active ingredient and, optionally, any membrane additives in the solution obtained in (a),

- (c) causing coacervation of the coating polymer in the suspension obtained in (b) by means of phase separation, thus obtaining cores coated with a polymeric membrane incorporating the active ingredient,
- (d) if necessary, subjecting the microcapsules to a hardening treatment of
5 membrane,
- (e) preferably washing and recovering the microcapsules thereby obtained.
- In step (a) the solvent or mixtures of solvents used to form the solution must be able to dissolve the polymer but not the active ingredient and the membrane additives, which remain dispersed in the form of solid particles in suspension.
- 10 The coating polymer may be either soluble or insoluble in water. A preferred water-insoluble polymer for use in the present invention is ethylcellulose; while preferred water-soluble polymers are gelatine, cellulose acetate phthalate or hydroxypropylmethylcellulose phthalate (HP55) or derivatives thereof.
- If the coating polymer used is insoluble in water, a particularly preferred solvent to
15 be used in step a) is cyclohexane; instead, if working with water soluble polymers, the preferred solvent is usually water at a pH between 1 and 9 and preferably between 4 and 7. The pH is preferably stabilised for example by means of a buffer.
- In step (b), the cores, the active ingredient and any membrane additive are added
20 to the polymer solution under stirring; the order in which the different components are added is not determining.
- Step a) and step b) may be also carried out as a single step, that is by addition of the polymer, the cores, the active ingredient and any membrane additive to solvent under stirring.
- 25 According to the present invention with the term "active ingredient" is meant any active ingredient with biological activity, in particular pharmaceuticals, also including mixtures of two or more of these. Non limiting examples of pharmaceuticals that may be used according to the present invention are: bronchodilating agents, CNS stimulants, antidepressants, anti-inflammatories,
30 antispasmodics and antiulceratives.

The membrane additives have solubility characteristics opposed to those of the membrane: in the case of water-soluble membranes, additives that are insoluble in water are used; in the case of membranes insoluble in water, water-soluble additives are used. Examples of preferred water soluble additives are lactose, mannitol, polyvinylpyrrolidone, hydroxypropylmethylcellulose, methylcellulose, hydroxypropylcellulose, swelling agents such as carboxymethylamide, croscarmellose, crospovidone, pregelatinized starch. Other examples may be pH modifiers such as dibasic sodium phosphate, citric acid, tartaric acid, fumaric acid, potassium hydrogen phosphate; once in contact with the dissolution means, these produce a pH (ranging from 1 to 9, more preferably from 2 to 7.5). Among the additives insoluble in water we may cite calcium and magnesium salts such as dibasic calcium phosphate, calcium sulphate, barium sulphate, calcium carbonate, magnesium carbonate, silicates.

In step (c), phase separation can take place by means of various techniques, per se known, such as temperature or pH variation or by adding substances, said phase-separation inducing agents, that modify the solubility equilibrium characteristics of the coating polymer dissolved and thus cause its insolubilisation. The technique used to obtain phase separation varies depending on the solvent in which the micro-encapsulation is carried out.

More specifically, in case the micro-encapsulation is carried out in an organic solvent the active ingredient, previously dispersed together with the cores and with any membrane additives, is subjected to cooling. During the cooling phase, through the effect of separation of the polymer the active ingredient remains incorporated in the form of solid particles into the gellified layer of the polymer together with any additives added in a mixture with it.

In the case of microencapsulation in an aqueous environment, after having suitably dissolved the polymer, for example CAP in a phosphate buffer, the cores are dispersed and the active ingredient is added under stirring at a constant speed. In this case phase separation is obtained by means of variations in the pH and/or temperature or by adding phase-separation inducing agents to the solutions. According to a preferred embodiment of the present invention phase

separation is performed by progressively adding a phase-separation inducing agent, for example a saturated solution of sodium sulphate, observing the solution separating and becoming viscous, an indication that the polymer has separated.

In the optional step (d) the microcapsules are subjected to a hardening treatment
5 of the membrane; these treatments are per se known and produced for example, in case of microencapsulation in an aqueous environment by adding citric acid while in case of encapsulation in an organic environment by cooling to ambient temperature.

The amount of polymer, its nature and any additives introduced contribute towards
10 regulating release of the active ingredient making it possible to modulate the degree of taste masking and/or modified release.

In step (e) the microcapsules are preferably washed to eliminate any excess residues of reagent, and after suitable decantation are recovered for example by filtration and then dried.

15 If necessary, one or more further protective coating layers may be applied on the microcapsules of the invention.

The present invention also relates to new microcapsules obtainable by the above described process. The microcapsules of the invention comprise cores coated with a polymer membrane wherein an active ingredient and, if required,
20 membrane additives are dispersed in the form of solid particles

The core preferably constitutes 50-95%, or more preferably 60-70% by weight of the microcapsule. It has a dimension ranging from 50 to 1200 μm , preferably from 100 to 500 μm .

The main function of the core is to provide a uniform and reproducible substrate
25 suitable for microencapsulation; any core that satisfies the aforesaid dimensional requirements may be used in the present invention (for example, microgranules, granules, pellets, etc.); preferred cores are non-pareil seeds, which, by means of the essentially regular spherical shape, allow uniform encapsulation with the coating polymer.

30 The core is essentially constituted by inert excipients, also mixed with one another, for example sucrose, lactose, microcrystalline cellulose, starch, talc, gum

arabic, glyceryl monostearate, glyceryl behenate, etc.. The cores preferably have no active ingredients; nonetheless, in some case it is also possible to use cores inside which an active ingredient is dispersed; this is useful for example when wishing to load high amounts of active principle and/or modulate release over a longer period of time; in these cases the microcapsule will not only contain the active ingredient in the wall of the coating, but also inside the core.

The polymer that constitutes the coating membrane represents in general from 2 to 40% by weight of the microcapsule, preferably from 2 to 20%.

The membrane may be soluble or insoluble in water; in micro-encapsulation with an insoluble membrane, the preferred coating polymer is ethylcellulose; in microencapsulating with a soluble membrane the most suitable polymer can be chosen for example from gelatine, cellulose acetate phthalate (CAP) or hydroxypropylmethylcellulose phthalate (HP 55) and derivatives thereof.

The particles of active ingredient contained in the membrane have a smaller mean diameter than the diameter of the core and are dispersed in the polymer membrane that coats the microcapsule in the form of solid particles.

The active ingredient particles preferably have dimensions ranging from 0.1 to 80 μm , more preferably from 1 to 30 μm ; the active ingredient is contained in the microcapsules in a percentage by weight preferably ranging from 0.1 to 40%, more preferably from 0.2 to 21 % by weight of the microcapsule.

The present inventors have surprisingly found that the coacervation process of the invention allows to obtain microcapsules that present a different distribution of the active principle in the membrane layer depending on the type of polymer utilised. Furthermore, the present inventors have surprisingly found that, by modulating the type and amount of polymer used in the process of the invention, it is possible to obtain microcapsules wherein the taste of the active principle is masked and/or its release modified without the need for further coating layers.

In the case of microencapsulation with a water-soluble polymer, the microcapsules obtained with the process of the invention are characterised by the fact that the active ingredient particles are prevalently disposed at the interface between the polymer and the core. In fact, as can be seen in Figure 1, in this case

the particles of active principle are distributed within the polymeric wall with a concentration that decreases progressively moving from the core towards the distal part of the membrane that may become essentially null at the level of the external surface.

- 5 This type of microcapsules have the advantage that they may be used for obtaining a taste masking effect, due to the absence of active principle in the distal part of the membrane and a modified release without the need for further protective layers. The modified release, in particular delayed release, which is attained with the polymers used in the present invention, depends on the amount and type and of polymer. The same polymers are also effective in taste masking application.

- 10 It is also important to stress that the aforesaid separation of the pharmaceutical inside the membrane does not influence the homogeneity of distribution of the pharmaceutical on the cores; in fact, the deposition percentage of the active ingredient on each surface unit of the core remains essentially constant in the entire batch subjected to microencapsulation, thus guaranteeing the necessary uniformity of dosage on the surface of the cores.

- 15 In case the microencapsulation is carried out using a water-insoluble polymer microcapsules are obtained wherein the particles of active principle are homogeneously dispersed within the coating membrane (Figures 2 and 3).

- 20 As demonstrated in the Examples below, in this case it is possible to obtain microcapsules with a modified release or/and taste masking. Both the amount of polymers and the presence of additives influence the dissolution rate of the active principle, thus attaining the desired modified release and/or taste masking.

- 25 Besides the pharmaceutical and the coating polymer, the membrane may also contain membrane additives useful to modulate the characteristics, for example permeability, mechanical resistance, plasticity, or to correct the organoleptic aspects (colour, odour, taste). The membrane additives have solubility characteristics opposed to those of the membrane: in the case of water soluble membranes, additives that are insoluble in water are used; in the case of
30 membranes insoluble in water, water soluble additives are used. Examples of

water soluble additives are lactose, mannitol, polyvinylpyrrolidone, hydroxypropylmethylcellulose, methylcellulose, hydroxypropylcellulose, swelling agents such as carboxymethylamide, croscarmellose, crospovidone, pregelatinized starch. Other examples may be pH modifiers such as dibasic sodium phosphate, citric acid, tartaric acid, fumaric acid, potassium hydrogen phosphate; once in contact with the dissolution means, these produce a pH (ranging from 1 to 9, more preferably from 2 to 7.5). Among the additives insoluble in water we may cite calcium and magnesium salts such as dibasic calcium phosphate, calcium sulphate, barium sulphate, calcium carbonate, magnesium carbonate and silicates.

Some of the above additives, for example, polyvinylpyrrolidone may also affect the dissolution rate of the active ingredient.

The membrane additives have a smaller mean diameter than the diameter of the cores, preferably ranging from 0.1 to 80 μm , more preferably from 7 to 30 μm , and preferably constitute from 2 to 20% by weight, more preferably from 3 to 10 % by weight of the microcapsule.

A further coating can be performed to further modulate the release of the active ingredient. The material used for the coating layers and the process for their application are those well known to the experts of the field.

With the instant invention, deposition of reproducible quantities of active ingredient on the surface of pharmaceutical cores has thus been attained using an easy to produce process; this procedure has proved to be reliable even when the pharmaceutical to be incorporated is present in low doses; moreover, microcapsules may be obtained wherein the taste of the active principle has been masked and/or its release modified without the necessity of applying further coating layers.

The present invention is now illustrated by means of the following non-limiting examples.

EXPERIMENTAL PART

Example 1

- At 80°C dissolve the ethylcellulose (10 parts) and polyethylene (20g) in cyclohexane (1000 parts) and disperse therein the MCC cores (Celphere FMC) (184 parts). Under stirring add ground Caffeine (D 4.3 = 25 µm) (4 parts), polyvinylpyrrolidone (2 parts). Again under stirring cool slowly to ambient temperature. The microcapsules obtained are separated by decantation, filtered and dried.

Example 2

- 10 Dissolve ethylcellulose (12 parts) and polyethylene (20g) in cyclohexane (1000 parts) at 80°C and disperse therein the MCC cores (Cellets PHARMATRANS) (172 parts), under stirring add Metoclopramide hydrochloride (D 4.3 = 30µm) (12 parts) and mannitol (4 parts). Again under stirring cool to ambient temperature. The microcapsules obtained are separated, filtered and dried.

Example 3

- 15 Dissolve the cellulose acetate phthalate (CAP) (140 parts) in water (6000 parts) containing a buffer mixture constituted by sodium and /or potassium phosphates and create a pH ranging from 6.0 to 6.5 with ionic strength of 0.5.
- Disperse the cores, 700 parts, constituted by granules or pellets, based on insoluble inorganic salts and binding substances such as triglycerides of fatty organic acids, obtained by granulation; add under stirring Ibuprofen, (160 parts) of dimensions ranging from 10 to 30 µm.

- 20 Add the phase-separation inducing agent, constituted by a 20% solution of sodium sulphate to promote phase separation of the CAP, then add a solution of citric acid to cause hardening of the membrane. Separate by filtering and dry the microcapsules obtained.

- 25 The microcapsules obtained, when analysed with an electronic microscope (Fig 1), show a distribution of the particles of the active principle within the polymeric membrane in the form of solid particles that are prevalently disposed at the interface between the polymer and the core.
- 30

Example 4

Dissolve the ethylcellulose 100STD p (30g) and polyethylene (60g) in cyclohexane (3000 g) at high temperature and disperse therein the inert cores (273g) (size 350 μm); under stirring add anhydrous micronised theophylline (60g).

- 5 Again under stirring cool slowly to ambient temperature. The microcapsules obtained are separated by decantation, washed, filtered, and dried.

A dissolution test is carried out on the microcapsules thus obtained comparing them with anhydrous theophylline in crystalline form.

///	Dissolution % at pH 6.8			
Assay(mg active principle/g microcapsule)	5 min	15 min	30 min	60 min
160 mg/g	18	41	60	83
Anhydrous Theophylline 160 mg	65	100	//	//

- 10 The results obtained in the dissolution test demonstrate that a modified release was obtained with the microencapsulation. The dissolution test was performed according to USP 26.

Example 5

Dissolve the ethylcellulose 100STD p (30g) and polyethylene (60g) in

- 15 cyclohexane (3000 g) at high temperature and disperse therein the inert cores (273g) (size 500 μm) , under stirring add anhydrous micronised theophylline (60g). Again under stirring cool slowly to ambient temperature. The microcapsules obtained are separated by decantation, washed, filtered, and dried.

Example 6

- 20 Dissolve the ethylcellulose 100STD p (8g) and polyethylene (20g) in cyclohexane (1000 g) at high temperature and disperse therein the inert cores (92g) (size 200 μm), under stirring add anhydrous micronised theophylline (17g) and polyvinylpyrrolidone CL (3g). Again under stirring cool slowly to ambient

temperature. The microcapsules obtained are separated by decantation, washed, filtered, and dried.

Example 7

- A dissolution test is carried out on the microcapsules obtained in Examples 5 and 6 according to the method previously described for Example 4

example	////	Dissolution % at pH 6.8			
	Assay	5 min	15 min	30 min	60 min
6	159 mg/g	18	37	55	75
	Assay	10 min	20 min	30 min	60 min
7	142 mg /g	28	64	84	94
	Anhydrous theophylline 160 mg	100	//	//	//

The dissolution test demonstrate that by introducing an additive (Ex. 7) it is possible to further modify the release.

Example 8

- 10 Dissolve the ethylcellulose 100STD p (22g) and polyethylene (60g) in cyclohexane (3000 g) at high temperature and disperse therein the inert cores (273g) (size 350 μ m), under stirring add caffeine (60g). Again under stirring cool slowly to ambient temperature. The microcapsules obtained are separated by decantation, washed, filtered, and dried.
- 15 The microcapsules obtained, when analysed with an electronic microscope (Fig 3), show a distribution of the particles of the active principle within the polymeric membrane in the form of solid particles that are prevalently disposed at the interface between the polymer and the core. A dissolution test is carried out on the microcapsules thus obtained compared to caffeine raw material showing the
- 20 modified release obtained.

///	Dissolution % at pH 1.2			
Assay	60 min	120 min	240 min	480 min
169 mg/g	47	57	68	71
Caffeine 170 mg	100			

Dissolution test was performed according to USP 26.

Example 9

Dissolve the ethylcellulose 100STD p (8g) and polyethylene (20g) in cyclohexane (1000 g) at high temperature and disperse therein the inert cores (92g) (size 100 μ m), under stirring add omeprazole (17g) and polyvinylpyrrolidone CL (3g). Again under stirring cool slowly to ambient temperature. The microcapsules obtained are separated by decantation, washed, filtered, and dried.

Example 10

A dissolution test is carried out on the microcapsules obtained in Example 9 showing the influence of the particle size of the inert core on the modified release.

		Dissolution % at pH 6,8			
example	Assay	30 min	60 min	120 min	240 min
9	190 mg/g	13	20	27.5	38

Dissolution test was performed according to USP 26

Example 11

Dissolve the ethylcellulose 100STD p (5g) and polyethylene (20g) in cyclohexane (1000 g) at high temperature and disperse therein the inert cores (77g) (size 200 μ m), under stirring add fluoxetine (6g) and polyvinylpyrrolidone CL (3g). Again under stirring cool slowly to ambient temperature. The microcapsules obtained are separated by decantation, washed, filtered, and dried.

The microcapsules obtained, when analysed with an electronic microscope (Fig 2), show a homogeneous distribution of the particles of the active principle within the polymeric membrane in the form of solid particles.

A dissolution test is carried out on the microcapsules thus obtained compared to fluoxetine raw material.

The very low amount dissolved after 5 min indicates the achievement of a taste masking effect due to the coating polymer.

Example	Assay	Dissolution % at pH 6,8				
		5 min	10 min	20 min	30 min	60 min
11	67 mg/g	2	76	85	90	95
Fluoxetine	60 mg	55	75	100		

Dissolution test was performed according to USP 26.

CLAIMS

1. Method of preparing microcapsules containing at least one active ingredient comprising the application of a polymeric membrane containing at least one active ingredients and, optionally, at least one membrane additive to a core having
5 dimensions ranging from 50 to 1200 μm wherein said application is carried out by the process of coacervation by means of phase separation.
2. Method as claimed in claim 1 comprising the following steps:
 - (a) forming a solution of the coating polymer in an aqueous or in organic solvent;
 - (b) suspending the cores, the particles of active ingredient and, optionally, any
10 membrane additive in the solution obtained in (a),
 - (c) causing coacervation of the coating polymer in the suspension obtained in (b) by means of phase separation,
 - (d) optionally, subjecting the microcapsules to a hardening treatment of the membrane.
- 15 (e) recovering the microcapsules thereby obtained.
3. Method as claimed in claim 2 wherein step a) and b) are carried out as a single step.
4. Method as claimed in claims 1 to 3, wherein said polymer is insoluble in water.
- 20 5. Method as claimed in claim 4 wherein said polymer is ethylcellulose.
6. Method as claimed in claim 4 or 5 wherein the solvent used in step a) is cyclohexane.
7. Method as claimed in claim 4 to 6 wherein the additive added in step b) is selected from lactose, mannitol, polyvinylpyrrolidone,
25 hydroxypropylmethylcellulose, methylcellulose, hydroxypropylcellulose, swelling agents such as sodium carboxymethylamide, croscarmellose, crospovidone, pregelatinized starch and pH modifiers
8. Method as claimed in claims 1 to 3, wherein said polymer is soluble in water.
9. Method as claimed in claim 8 wherein said polymer is selected from the group
30 consisting of gelatine, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate or derivatives thereof.

10. Method as claimed in claim 8 or 9, wherein the solvent used in step a) is water at a pH comprised between 1 and 9.
11. Method as claimed in claim 10, wherein the pH is comprised between 4 and 7.
12. Method as claimed in claims 8 to 11, wherein the additive added in step b) is
5 selected from dibasic calcium phosphate, calcium sulphate, barium sulphate, calcium carbonate, magnesium carbonate and silicates.
13. Method as claimed in claims 4 to 7, wherein in step c) phase separation takes place by variation in temperature.
14. Method as claimed in claim 8 to 12, wherein in step c) phase separation takes
10 place by pH variation, variation in temperature or insolubilisation of the polymer by adding phase-separation inducing agents.
15. Microcapsules comprising a core having dimension ranging from 50 to 1200 μm and a coating consisting of a polymeric membrane containing at least one active ingredient dispersed therein in the form of solid particles, wherein the
15 polymer constituting the membrane is a water-soluble polymer and the particles of active ingredient are dispersed inside said polymeric membrane with a concentration that decreases progressively moving from the core towards the distal part of the membrane.
16. Microcapsules as claimed in claim 15 wherein the taste of the active
20 principle is masked.
17. Microcapsules as claimed in claims 15 or 16 characterised by a modified release of the active principle.
18. Microcapsules as claimed in claim 17 wherein said modified release is a delayed release.
- 25 19. Microcapsules as claimed in claims 15 to 18, wherein the water-soluble polymer is chosen from gelatine, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and derivatives thereof.
20. Microcapsule as claimed in claims 15 to 19, wherein said polymeric membrane further contains water-insoluble membrane additives.
- 30 21. Microcapsules constituted by a core having dimension ranging from 50 to 1200 μm and coated with a polymeric membrane comprising one or more active

ingredients homogeneously dispersed thereof in the form of solid particles, characterised in that the polymer constituting the membrane is a water-insoluble polymer.

22. Microcapsules as claimed in claims 21 characterised by a modified release
5 of the active ingredient.

23. Microcapsules as claimed in claims 21 or 22, wherein the water-insoluble polymer is selected from ethylcellulose and its derivatives.

24. Microcapsules as claimed in claims 21 to 23, wherein the polymeric membrane further contains water-soluble additives.

10 25. Microcapsules as claimed in claims 15 to 24, wherein the active ingredient has dimensions ranging from 0.1 to 80 μm , and ranges from 0.1 to 40% by weight of the microcapsules.

26. Microcapsules as claimed in claim 25, wherein the active ingredient has dimensions ranging from 1 to 30 μm , and ranges from 0.2 to 21% by weight of the
15 microcapsules.

27. Microcapsules as claimed in claims 15 to 26, wherein the core constitutes 50 to 95% by weight of the microcapsules and the coating polymer varies from 2 to 20% by weight of the microcapsule.

28. Microcapsules as claimed in claims 15 to 27, wherein the membrane contains
20 additives having a mean diameter ranging from 0.1 to 80 μm and constituting from 2 to 10% by weight of the microcapsule.

29. Microcapsules as claimed in claim 28, wherein the membrane additives have a mean diameter ranging from 7 to 30 μm and constitute from 3 to 5% by weight of the microcapsule.

25 30. Microcapsules as claimed in claims 15 to 29 coated with a further coating layer.

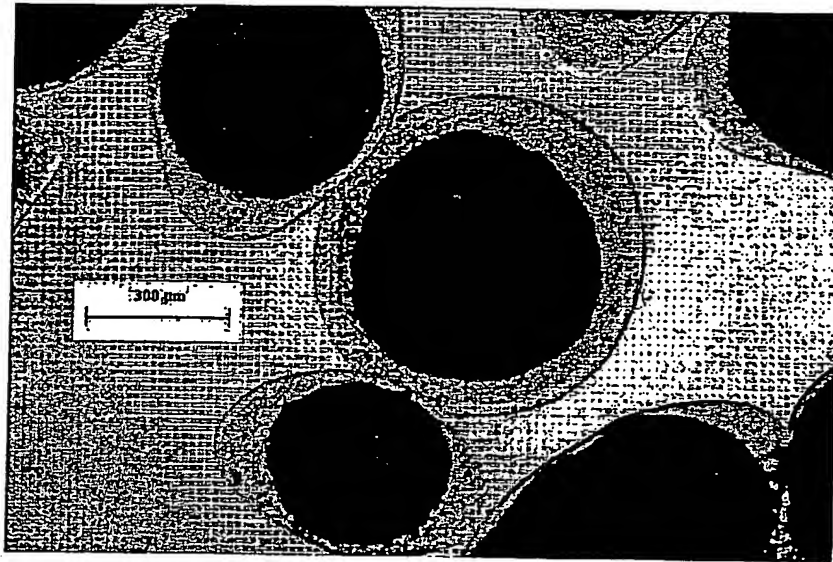


FIGURE 1

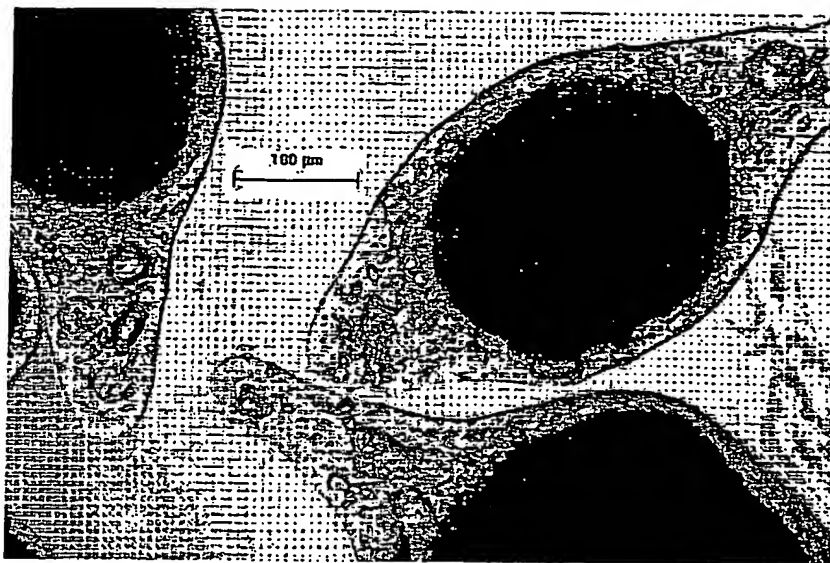


FIGURE 2

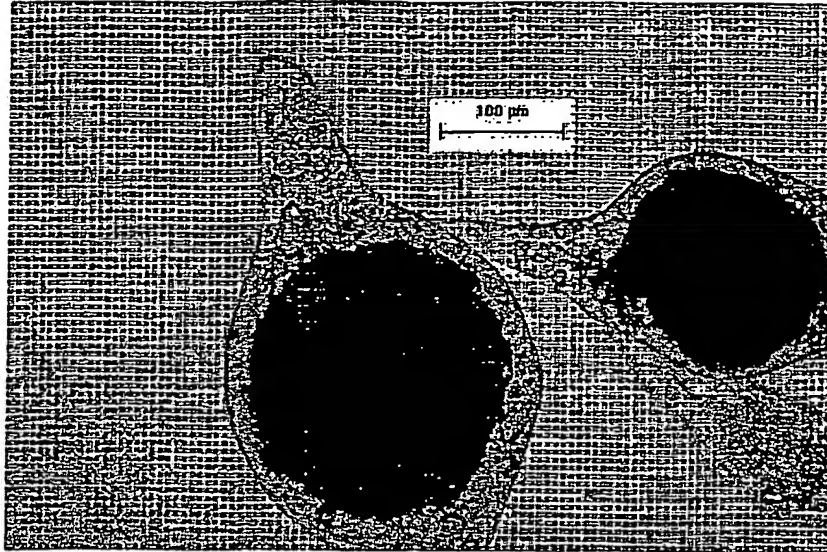


FIGURE 3

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